Amendment to the Drawings

The attached sheet of drawings, which includes Figure 4, replaces the original sheet including Figure 4. In the attached sheet, the background of Figure 4 has been lightened.

Attachment: Replacement Sheet for Figure 4.

REMARKS

Reconsideration of the allowability of the present application in view of the above amendments and the following remarks is requested respectfully.

Status of the Claims

Claims 1-3, 5, 7, and 19-41 were acted upon by the Examiner. Claim 19 has been withdrawn from consideration. Claims 1-3, 5, 7, 20, 21 and 26-41 have been rejected. Claims 22-25 have been deemed allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 3 and 7 are amended. Claim 3 is amended to eliminate subpart (c). In light of the very short sequences recited in subpart (a), subpart (c) was superfluous (i.e., even a single amino acid change would have been less than 95% identical). Claim 7 is amended to replace "has" with "consists of."

Summary of the Objections/Rejections

The drawings have been objected to because the background of Figure 4 is too dark. Claims 1-3, 20, 26, 28, 30, 32, 34, 36, 38, and 40 have been rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. Claims 1-3, 5, 7, 20-21, and 26-41 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. There are no present novelty or obviousness rejections under 35 U.S.C. §§ 102, 103.

Applicants' Invention

The present invention relates to a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment by administering certain fusion polypeptides that contain soluble CD39 having apyrase activity. Apyrases catalyze the hydrolysis of nucleoside tri- and/or di- phosphates.

ADP is a powerful agonist of platelet activation and recruitment. Applicants have demonstrated that CD39 is an ecto-ADPase (apyrase) responsible for inhibition of platelet function. To study the effects of CD39, Applicants have generated a number of fusion polypeptides comprising soluble CD39. Applicants have tested some of these constructs for their effectiveness in inhibiting platelet activation and recruitment *in vitro*, *ex vivo*, and *in vivo*. Applicants have also correlated the apyrase activity of the fusion polypeptides with their biological activity *in vivo*.

Applicants have made the unexpected discovery that the addition of one or more amino acids added to the N-terminus of a soluble CD39 polypeptide results in improved expression levels, stability and/or activity of the CD39 polypeptide. Based on this discovery, Applicants have devised a method of using these fusion polypeptides for inhibiting platelet activation and recruitment in a mammal.

Discussion of Drawings Objection

The Examiner has objected to Figure 4 as being too dark. Applicants enclosed another copy of Figure 4 with their last Reply. See attached copy of stamped postcard. Applicants, however, enclose with this Reply another copy of Figure 4.

Discussion of New Matter Rejections

Claims 1-3, 20, 26, 28, 30, 32, 34, 36, 38, and 40 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner has indicated that this is a new matter rejection.

The Examiner asserts that the recitation "amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, and amino acids 21-24 of SEQ ID NO:30" in claims 1 and 3 represents a departure from the specification and the claims as originally filed and that applicant's citation to the specification does not provide support for this recitation. Applicants' traverse respectfully this rejection.

Each of these particular groups of amino acids was fused to a soluble portion of CD39 ("solCD39") in certain constructs disclosed in the specification. During the expression of these fusion constructs in recombinant cells the N-terminal leader sequence is cleaved. It is the post-cleaved constructs that are isolated from the culture media and tested in the assays described in the specification, and thus, it is the post-cleaved constructs that are used in applicants' claimed methods. The specification describes both the pre- and post-cleaved amino acid sequences for the fused polypeptides by indicating the cleavage point in the amino acid sequence. Each one of these sequences is disclosed in the specification as being fused to a soluble portion of CD39 as follows:

- amino acids 1-15 of SEQ ID NO:6 (APTSSSTKKTQLTSS) – see page 39, line 6 (in the specification, the asterisk indicates the cleavage point and TQNK is the first four amino acids of solCD39); see also page 36, line 36 to page 37, line 5 (amino acids 1-24 of SEQ ID NO:7 is the pre-cleaved N-terminal portion and amino acids 25-39 of SEQ ID NO:7 are equivalent to amino acids 1-15 of SEQ ID NO:6);
- amino acids 25-35 of SEQ ID NO:28 (ASTKKTQLTSS) – see page 39, line 9 (in the specification, the asterisk indicates the cleavage point and TQNK is the first four amino acids of the fused solCD39);
- amino acids 27-34 of SEQ ID NO:29 (KKTQLTSS) – see page 39, line 11 (in the specification, the asterisk indicates the cleavage point and TQNK is the first four amino acids of the fused solCD39);

- amino acids 21-24 of SEQ ID NO:30 (APTS) – see page 40, line 13 (in the specification, the asterisk indicates the cleavage point and TQNKALPE is the first eight amino acids of the fused solCD39).

With respect to the amino acids 1-15 of SEQ ID NO:6, applicants note that the specification on page 39 refers to SEQ ID NO:11 which is simply the pre-cleaved N-terminal portion of SEQ ID NO:6. Compare amino acids 25-39 of SEQ ID NO:11 with amino acids 1-15 of SEQ ID NO:6 Because SEQ ID NOS. 28, 29 and 30 contain the pre-cleaved amino acid sequences, it was necessary for applicants to recite only a portion of these sequences in the claims. Thus, each of these sequences is described in the specification as being fused to solCD39. Accordingly, this new matter rejection should be withdrawn.

The Examiner also asserts that the recitation "39-476 of SEQ ID NO:2" in claim 2 represents a departure from the specification and the claims as originally filed. This is clearly not new matter as this recitation is in claim 2 as originally filed. Accordingly, this new matter rejection should be withdrawn.

Discussion of Written Description Rejection

Claims 1-3, 5, 7, 20-21 26-41 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse respectfully this rejection.

Claim 5 and its Dependent Claims

With respect to claim 5 and its dependents (claims 7, 21, 27, 29, 31, 33, 35, 37, 39, and 41), the Examiner asserts that the specification does not reasonably provide a written description of "any soluble CD39 polypeptide selected from the group consisting of amino acids 25-474 of SEQ ID NO: 28, amino acids of 27-473 of SEQ ID NO: 29 and amino acids 21-463 of SEQ ID

NO: 30 for the claimed method of inhibiting platelet activation and recruitment." These claims, however, cover constructs that were *specifically disclosed* in the application.

For example, the solCD39 construct that contains amino acids 25-474 of SEQ ID NO: 28 is disclosed in the specification at page 39, line 9 (the first 24 amino acids before the asterisk are cleaved from the construct). Moreover, the specification explains that the polypeptide encoded by this construct has "the sequence SEQ ID NO:28" and that "residues 36-474 are a soluble portion of CD39 and the predicted cleavage of the leader sequence is between Ser24 and Ala25." See page 39, lines 14-16. Accordingly, the post-cleaved sequence contains the amino acids 25-474 of SEQ ID NO: 28 as recited in claim 5.

Similarly, the solCD39 construct that contains amino acids 27-473 of SEQ ID NO: 29 is disclosed in the specification at page 39, line 11 (the first 26 amino acids before the asterisk are cleaved from the construct). Moreover, the specification explains that the polypeptide encoded by the this construct has the "sequence SEQ ID NO:29" and that "residues 35-473 are a soluble portion of CD39 and the predicted cleavage of the leader sequence is between Thr26 and Lys27." See page 39, lines 16-18. Accordingly, the post-cleaved sequence contains the amino acids 27-473 of SEQ ID NO: 29 as recited in claim 5.

Likewise, the solCD39 construct that contains amino acids 21-463 of SEQ ID NO: 30 is disclosed in the specification at page 40, line 13 (the first 20 amino acids before the asterisk are cleaved from the construct). Moreover, the specification explains that the polypeptide encoded by this construct has the "sequence SEQ ID NO:30" and that residues 25-463 are a soluble portion of CD39 and the predicted cleavage of the leader sequence is between Gly20 and Ala21." See page 40, lines 16-18. Accordingly, the post-cleaved sequence contains the amino acids 21-463 of SEQ ID NO: 30 as recited in claim 5.

The Examiner asserts further that use of the term "has" is open-ended in claim 7 and that there is no disclosure regarding which amino acids may be added to the residues 21-463 of SEQ ID NO:30. In response and without prejudice, applicants have amended claim 7 to state that "the soluble CD39 polypeptide *consists of* the sequence of amino acids 21-463 of SEQ ID NO: 30."

Moreover, the Examiner concedes that the specification discloses "a method for inhibiting platelet activation and recruitment by administering the specific soluble human CD39 [constructs] such as the ones disclosed at page 37-40 of the specification." As discussed above, claim 5 recites the sequences disclosed on pages 39-40 of the specification. These constructs are produced by recombinant cells and are cleaved prior to being secreted into the culture medium. Thus, the post-cleaved constructs are the sequences that would be used in any claimed method. As discussed in detail above, the specification describes both the pre- and post-cleaved sequences. Applicants have, thus, shown possession of the invention. See M.P.E.P. § 2163.02 ("An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997)."). Accordingly, this rejection should be withdrawn.

Claim 1 and its Dependent Claims

With respect to claim 1 and its dependents (claims 2-3, 20, 26, 28, 30, 32, 34, 36, 38, and 40), the Examiner asserts that the specification does not reasonably provide a written description of the full scope of claim 1.

Claim 1 is directed to a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment comprising administering an effective amount of a soluble CD39 polypeptide consisting of a structure X-Y. Claim 1 recites that X is defined as an Ala residue, amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids

27-34 of SEQ ID NO:29, or amino acids 21-24 of SEQ ID NO:30. Y is defined as (a) amino acids 36-478 of SEQ ID NO:2, (b) consecutive sequences of amino acids 36-478 of SEQ ID NO:2 with apyrase activity, (c) a variant polypeptide 95% identical in sequence to amino acids to (a) or (b); or (d) a polypeptide of (a), (b) or (c) with at least one conservative amino acid substitution.

Applicants have adequately described the X portion of the X-Y construct of claim 1 as discussed above – amino acids 1-15 of SEQ ID NO:6 (APTSSSTKKTQLTSS) is disclosed on page 39, lines 6; amino acids 25-35 of SEQ ID NO:28 (ASTKKTQLTSS) is disclosed on page 39, line 9; amino acids 27-34 of SEQ ID NO:29 (KKTQLTSS) is disclosed on page 39, line 11; amino acids 21-24 of SEQ ID NO:30 (APTS) is disclosed on page 40, line 13. With respect to subpart (a) of claim 1, these amino acids are simply the soluble portion of CD39 as disclosed in Figure 2. While the constructs disclosed on pages 39-40 use a somewhat shorter sequence (38-476 of SEQ ID NO:2), applicants have disclosed that the invention encompasses "amino acids added to the N-terminus of a *soluble CD39 polypeptide* in order to improve the expression levels and/or stability of the CD39 polypeptide." See page 11, lines 21-23. Moreover, the specification as filed discloses that the soluble CD39 polypeptides have the amino acid sequence as set forth in Figure 1 (SEQ ID NO:2) wherein the amino terminus is selected from the group consisting of amino acids 36-44, and the carboxy terminus is selected from the group consisting of amino acids 471-478. See page 2, lines 33-36. Thus, the specification clearly disclose a polypeptide consisting of amino acids 36-478 of SEQ ID NO:2.

With respect to subparts (b), (c), and (d) of claim 1, applicants have adequately described the polypeptides within the scope of these subparts by providing the amino acid sequence in the sequence listing as filed (SEQ ID NO:2). The written description requirement does not require a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988). In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002), the Federal Circuit made clear that the written description

requirement can be satisfied in a number of ways by disclosing, for example, "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." Particularly relevant to this case, the Board of Patent Appeals and Interferences recently recognized that a claim drawn to a naturally occurring polypeptide that is at least 95% identical to a disclosed sequence is adequately described by the specification. *Ex parte Bandman*, Appeal No. 2004-2319 at p. 5 (BPAI 2005) (enclosed with prior Reply).

Here, Applicants have provided the complete structure of SEQ ID. NO:2. Applicants have also disclosed the putative domain of soluble CD39 involved in apyrase activity. See Figure 2. Thus, with respect to subpart (b) one of skill in the art would be able to identify and verify, using the assays described in the specification, a consecutive amino acid sequence that has apyrase activity. With respect to subpart (c), applicants have provided guidance on page 10, lines 22-37 regarding how to select a polypeptide that is 95% identical to a given sequence. With respect to subpart (d), applicants have also provided on page 9, line 35 to page 10, line 4 of the specification a list of conservative amino acid substitutions. Moreover, such conservative substitutions were well-known in the art at the time this application was filed. Accordingly, applicants' disclosure of the structure in SEQ ID NO:2 coupled with the identity of the apyrase domain of CD39 and the assays to test apyrase activity is more than enough to adequately describe the polypeptides to one of skill in the art within the scope of claim 1.

Claim 3

With respect to claim 3, the Examiner asserts that the specification does not reasonably provide a written description of the full scope of claim 3.

Claim 3 is dependent upon claim 1 and, as amended, further defines X as (a) amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, and amino acids 21-24 of SEQ ID NO:30; (b) consecutive amino acids of such amino

acids wherein the resulting X-Y polypeptide has apyrase activity; and (c) such amino acids with at least one conservative amino acid substitution wherein the resulting X-Y polypeptide has apyrase activity.

With respect to subpart (a), each of these sequences is specifically disclosed in the specification as discussed with respect to claim 1. With respect to subparts (b) and (c) (formerly subpart (d)) of claim 3 and as discussed above, applicants have adequately described the polypeptides within the scope of these subparts by providing the amino acid sequence in the sequence listing as filed. One of skill in the art would be able to select consecutive amino acids from such sequences that when fused to soluble CD39 would retain apyrase activity. Moreover, using the guidance provided in the specification and the knowledge in the art at the time of filing, one of skill in the art would be able to identify conservative amino acid substitutions that would not destroy the apyrase activity of the fused polypeptide.

Accordingly, the written description rejections should be withdrawn.

Conclusion

In view of the proposed claim amendment and the arguments presented above, the present application is believed to be in condition for allowance and an early notice thereof is earnestly solicited. Applicants request that the Examiner contact the undersigned before issuing an advisory action.

Respectfully submitted,

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Docket No. P23,495 USA Atty. MGS/jmk

The Patent / Trademark Office is in receipt of the following:

- ☐ ~~Affidavit~~/Declaration, 37 CFR
- ☑ Amendment, ~~37 CFR~~ Transmittal Letter
- ☐ Amendment to allege use
- ☐ Appeal notice/Appeal brief
- ☐ Appointment of domestic representative
- ☐ Assignment & cover sheet
- ☐ Cert. of correction request
- ☐ Cert. of Exp. Mailing, Date
  No.
- ☑ Cert. of mailing, Dated April 12, 2006
- ☑ Charge deposit account, in duplicate PTO Form 2038
- ☐ Check $ for
- ☐ Demand for PCT examination
- ☑ Extension of time petition 3 months
- ☐ Extension of time to file Statement of Use
- ☐ IDS (information disclosure statement)
  PTO Form 1449: # of pages enc.
  # of references enc.
- ☐ Issue fee transmittal & advance order
- ☐ Letter
- ☐ Maintenance fee transmittal
- ☐ Opposition notice (in duplicate)
- ☐ Patent Application
  ____ # of pages ____ # of pages of claims
  ____ # of sheets of drawings
  ____ Declaration/Oath: ____ signed ____ unsigned
  ____ Transmittal letter

Title of Invention / Mark

- ☐ PCT Application, transmittal, request & fee sheet
- ☐ Petition under 37 CFR
- ☐ Petition for cancellation
- ☐ Power of attorney
- ☐ Priority claim
- ☐ Renewal application
- ☑ Reply ~~37 CFR~~ to Action of Oct. 17, 2005
- ☐ Request for extension of time to file opposition notice (in triplicate)
- ☐ Section 8/Section 15 Affidavit/Declaration
- ☐ Specimens
- ☐ Statement of use
- ☐ Trademark/Service Mark Application
  ____ Declaration
  ____ Power of attorney
  ____ Drawing
- ☐ Verified statement/Small entity
- ☐ Withdrawal
- ☑ Other Declaration of Aaron J. Marcus, M.D.
  Decision on Appeal of Final Rejection
  Appl. No. 09/915,694 - Appeal #2004-2319
  Figure 4 Drawing